

SIMVASTATIN

There are increasing reports to the Centre for Adverse Reaction Monitoring (CARM) of rhabdomyolysis due to interactions with simvastatin, resulting from serum concentrations of simvastatin increasing over 200 times. Important medicines to be wary of:

- **Itraconazole**
 - Serum concentration may increase up to 200-fold
 - Avoid combination.
- **Erythromycin and clarithromycin**
 - Serum concentrations may increase up to 80-fold
 - Avoid this combination
 - Limited data for roxithromycin. If used, ensure the patient is very aware to report **any** muscle aches.
- **Diltiazem and verapamil**
 - Serum concentrations may increase up to 60-fold
 - A relatively common combination, but many reports to CARM of simvastatin-induced rhabdomyolysis have the combination of simvastatin and diltiazem
 - Ensure the patient knows to report any muscle aches immediately
 - Check the lipid profile 4–6 weeks after the combination (plus ALT) and consider down titrating the simvastatin if the lipid profile is particularly low.
- **Amiodarone**
 - There are increasing reports that this is a significant interaction for some people.

WARFARIN

- **Erythromycin, clarithromycin and roxithromycin**
 - Increasing reports of high INR results, some resulting in hospitalisation
 - If the combination is really necessary, monitor the INR in 3 days.
- **Tramadol**
 - Increasing reports
 - If tramadol is used, it should be used consistently and monitor INR in 3 days, then 1 week if there was no change.
- **Amiodarone**
 - 20–60% increase in warfarin
 - Monitor INR weekly for 4 weeks (onset usually seen in 2 weeks).

SSRIS

- **Tricyclic antidepressants**
 - May get 40-fold increase in tricyclic antidepressant
 - Warn the patient about symptoms of serotonin syndrome / toxicity.
- **Tramadol**
 - The Australian Adverse Drug Reaction Centre has had an increasing number of reports of serotonin toxicity with the combination of tramadol and an SSRI, especially if in combination with a tricyclic antidepressants or an antipsychotic medicine.

TRIPLE WHAMMY

This is the combination of an **ACE Inhibitor (or angiotensin II antagonist)** plus **diuretic (or dehydration)** plus **NSAID (or COX-2 Inhibitor)** and is an important risk factor for renal failure, especially in the older person.

INTRODUCTION

Drug interactions can be broadly categorised as pharmacokinetic or pharmacodynamic. In pharmacokinetic interactions there is a change in the plasma concentration of the interacting drug which can lead to toxicity or sub-therapeutic effect. In a pharmacodynamic interaction there is a modification of pharmacological effect without a change in plasma concentration; for example, additive anticholinergic effects seen with amitriptyline and oxybutin or serotonin syndrome which can occur with an SSRI and tramadol. This resource mainly focuses on major pharmacokinetic drug interactions that may be seen in general practice and their management. It is not a comprehensive resource.

TABLE OF COMMONLY USED MEDICINES THAT INTERACT

The table has **interactions that are relatively common or carry a high risk of toxicity in red**, **moderate interactions in blue**, **minor interactions in green** and **interactions to be aware of in black**. The table quantifies the potential interaction by reporting what are generally the maximum potential increases in serum concentration. Where the percentage increase is given, e.g. 300% increase, then this means that the serum concentration may be increased threefold, which is similar to giving three times the dosage of the target medicine. Hence many of the interactions are dependent on the initial dosage of the target medicine. As an example, the interactions with simvastatin have become more significant with the higher dosages of simvastatin being used.

Because of the variability in individual metabolism, many interactions will not be obvious in most individuals, but when an interaction occurs, it may lead to considerable morbidity, or mortality. The usual way to manage the potential interaction is through conscientious monitoring and general awareness of the clinical symptoms of toxicity. If a new medicine has been added and a new symptom occurs, be suspicious of an interaction, not just an adverse effect.

MANAGING INTERACTIONS

Questions to ask when about to prescribe a potentially interacting medicine:

- Is the combination really necessary—what are the alternatives?
- What are the likely adverse effects of high dosages of the target medicine (how hazardous)?
- What clinical monitoring does the patient need to know about to report back to you?
- What objective monitoring needs to be done, and when?

THE RED ALERT DRUGS AND INTERACTIONS

The following medicines should 'ring alarm bells' as having important interactions:

- Warfarin
- Statins particularly simvastatin (not pravastatin)
- Macrolide antibiotics particularly erythromycin, clarithromycin (less with roxithromycin, minimal with azithromycin)
- Calcium channel blockers particularly diltiazem and verapamil
- Azole antifungals particularly itraconazole
- SSRIs particularly fluoxetine, paroxetine; less so citalopram
- Amiodarone
- Digoxin
- Cyclosporin
- Antiepileptic medicines particularly carbamazepine, phenytoin; less so valproate, gabapentin

REFERENCES

As well as searching the primary literature, the David Flockhart Interaction website was used for the cytochrome P450 enzyme table (www.drug-interactions.com) and Stockley's Drug Interactions textbook.

This table was developed for the Goodfellow Unit Symposium (2007) by Drs **Linda Bryant** (Clinical Advisory Pharmacist, Department of General Practice and Primary Health Care, University of Auckland; East Health PHO; and Comprehensive Pharmaceutical Solutions Ltd) and **Tana Fishman** (Senior Lecturer, Department of General Practice and Primary Health Care, University of Auckland), and further developed with assistance from **Robert Buckham** (Chief Drug Information Pharmacist, Christchurch Hospital) and **David Woods** (BPAC).

INTERACTING CLASS	INTERACTING DRUGS	Statins (not pravastatin)		Calcium channel blockers				Combined oral contraceptives	Tricyclic antidepressants	Cyclosporin Tacrolimus	Digoxin	Tramadol	Triazolam	Warfarin
		Atorvastatin	Simvastatin	Amlodipine	Diltiazem	Felodipine	Verapamil							
Macrolides Erythromycin is the most potent inhibitor. Roxithromycin has less inhibitory activity. Azithromycin minimal.	Erythromycin	30–40% increase. Monitor for muscle aches.	400–600% increase. Avoid combination.	Isolated cases. Monitor BP, swollen ankles.	150% increase. Monitor BP, swollen ankles.	250% increase. Monitor BP, swollen ankles.	Isolated cases. Monitor BP, swollen ankles.	Breakthrough bleeding reported. Avoid or take extra precautions	Unlikely interaction.	500–700% increase. Avoid combination. If unavoidable, reduce dosage to 35% and monitor cyclosporin.	200–400% increase. Unpredictable (~10% of patients). Avoid or monitor digoxin in 5–7 days.		Possible increase in serum concentration. Avoid or warn of increased sedation.	Small number of patients have increased INR. Avoid or monitor INR at 3–5 days.
	Clarithromycin	200–400% increase. Monitor for muscle aches.	1000% increase. Avoid combination.	No published reports but monitor BP, swollen ankles.	No published reports but monitor BP, swollen ankles.	No published reports but monitor BP, swollen ankles.	No published reports but monitor BP, swollen ankles.	Although low risk, high consequences. Use extra precautions.	Unlikely interaction.	200–1200% increase. Avoid combination.	200–400% increase. Unpredictable (~10% of patients). Avoid or monitor digoxin in 3–5 days.		Up to 500% increase in serum concentration. Avoid combination.	Small number of patients have increased INR. Avoid or monitor INR at 3–5 days.
	Roxithromycin	Limited reports and information. Less likely to interact. Monitor for muscle aches.	Limited reports of an interaction. Monitor muscle aches.	No published reports. Least likely macrolide to interact but monitor BP, swollen ankles.	No published reports. Least likely macrolide to interact but monitor BP, swollen ankles.	No published reports. Least likely macrolide to interact but monitor BP, swollen ankles.	No published reports. Least likely macrolide to interact but monitor BP, swollen ankles.	Although very low risk, high consequences. Use extra precautions.	Unlikely interaction.	50–60% increase. Avoid or monitor cyclosporin in 3–5 days.	200–400% increase. Unpredictable (~10% of patients). Avoid or monitor digoxin in 5–7 days.		Small increase in serum concentration.	Small number of patients have increased INR. Avoid or monitor INR at 3–5 days.
Calcium channel blockers Diltiazem and verapamil are potent inhibitors. Amlodipine, felodipine and nifedipine less so.	Amlodipine	No apparent interaction. Monitor muscle aches.	No apparent interaction. Monitor for muscle aches.		Expected additive action. Effect may be greater due to enzyme inhibition.	Not a rational combination.	Expected additive action. Effect may be greater due to enzyme inhibition.	Unlikely interaction	Unlikely interaction.	40% increase. Monitor cyclosporin, renal function, BP.		Unlikely interaction.	Unlikely interaction.	No apparent clinical effect.
	Diltiazem	Not reported, but potential increase. Monitor muscle aches.	200–500% increase. Monitor ALT (6 weeks) and muscle aches.	Expected additive action. Effect may be greater due to enzyme inhibition.		Expected additive action. Effect may be greater due to enzyme inhibition.	Expected additive action. Effect may be greater due to enzyme inhibition.	Unlikely interaction	Case reports of up to 200% increase. Monitor for increased sedation, blurred vision, postural hypotension.	150–300% increase. Monitor cyclosporin, renal function, BP.	150–300% increase possible. Monitor digoxin in 7–10 days.		200–300% increase. Warn about sedation and risk of driving.	No apparent clinical effect.
	Verapamil	400% increase. Monitor ALT (6 weeks) and muscle aches.	400–600% increase. Monitor ALT (6 weeks) and muscle aches.	Expected additive action. Effect may be greater due to enzyme inhibition.	Not a rational combination.	Expected additive action. Effect may be greater due to enzyme inhibition.		Unlikely interaction	Case reports of up to 200% increase. Monitor for increased sedation, blurred vision, postural hypotension.	150–300% increase. Monitor cyclosporin, renal function, BP.	150–300% increase possible. Monitor digoxin in 7–10 days.		Unlikely interaction.	No apparent clinical effect.
Azole antifungals Itraconazole is a particularly potent inhibitor. Fluconazole is a less potent inhibitor.	Fluconazole	Potential for an interaction. Be alert for muscle aches.	Potential for an interaction (has been reported). Be alert for muscle aches.	Unlikely to be clinically important. Be alert for swollen ankles.	Unlikely to be clinically important. Be alert for swollen ankles.	Unlikely to be clinically important. Be alert for swollen ankles.	Unlikely to be clinically important. Be alert for swollen ankles.	Contradictory information. High consequences. Use extra precautions.	Limited reports. Monitor for TCA adverse effects.	200–300% increase. Reduce dosage 70–80% and monitor .	Potential interaction. Monitor digoxin in 7–10 days.		200% increase in some cases. Warn about sedation, driving.	Increased INR in a number of people. Monitor INR after 3–5 days.
	Itraconazole	200–300% increase. Monitor ALT (6 weeks) and muscle aches.	1000–2000% increase. Avoid combination.	An interaction is likely. Also negative inotropic effect noted. Monitor BP, swollen ankles and cardiac function.	Significant increase plus negative inotropic effect. Reduce diltiazem. Monitor BP, swollen ankles, and cardiac function.	Significant increase plus negative inotropic effect. Monitor BP, swollen ankles and cardiac function.	An interaction is likely. Also negative inotropic effect. Monitor BP, swollen ankles and cardiac function.	Isolated cases of contraceptive failure. Avoid or use extra precautions.	Limited reports. Monitor for TCA adverse effects.	200–300% increase. Reduce dosage 70–80% and monitor .	200–400% increase but unpredictable. Monitor digoxin in 7–10 days.	Potential interaction – may increase tramadol concentrations. Monitor for ↑ ADRs, including serotonin toxicity.	200–300% increase in some cases. Warn about sedation, driving.	Only isolated cases reported. Monitor INR after 3–5 days.
SSRIs Fluoxetine and paroxetine are the most potent inhibitors. Citalopram is less likely to interaction, although there have been cases.	Fluoxetine	Unlikely interaction.	Small potential for an interaction. Monitor for muscle aches.	Isolated cases of interaction. Be alert for swollen ankles.	Isolated cases of interaction. Be alert for swollen ankles.	Isolated cases of interaction. Be alert for swollen ankles.	Isolated cases of interaction. Be alert for swollen ankles.	Unlikely interaction.	400%+ increase. Dose dependent. Warn about serotonin toxicity, increased seizure risk.	Isolated reports of interactions. Avoid and use an alternative antidepressant.	Isolated reports. Monitor for any gastrointestinal disturbances.	May increase seizure risk and reduce analgesia. Warn about serotonin toxicity. Care if also on a TCA.	No apparent interactions.	Unpredictable increase in INR. Monitor INR. Potential additive antiplatelet effect.
	Paroxetine	Unlikely interaction.	Unlikely interaction.	Unlikely interaction.	Unlikely interaction.	Unlikely interaction.	Unlikely interaction.	Unlikely interaction.	400%+ increase. Dose dependent. Warn about serotonin toxicity, increased seizure risk.			May increase seizure risk and reduce analgesia. Warn about serotonin toxicity. Care if also on a TCA.	No apparent interaction.	Isolated reports of increased INR. Monitor . Potential additive antiplatelet effect.
Antiepileptics Carbamazepine and phenytoin are potent enzyme inducers. Valproate, gabapentin and lamotrigine are less likely to cause an interaction.	Carbamazepine		Probable reduction in simvastatin concentration. Monitor lipid profile.	Potential reduction in amlodipine concentration. Monitor blood pressure.	40–400% increase in carbamazepine and phenytoin possible. Monitor serum concentrations in 7 days. Effect of diltiazem can be reduced. Check blood pressure.	Felodipine concentrations reduced. Check blood pressure control.	40%+ increase in carbamazepine and phenytoin possible. Monitor serum concentrations in 7 days. Effect of verapamil can be reduced. Check blood pressure.	Pregnancy risk. Spotting occurs in > 60%. Estimate failure rate 3.1 / 100 women years. Avoid or increase contraceptive dosage.	Concentration of the tricyclic antidepressant can be reduced but not usually clinically significant. (NB TCAs increase seizure risk)	Concentration of cyclosporin reduced. May need a 2- to 5-fold increase in dosage. Monitor serum cyclosporin or use alternative antiepileptic.	Unlikely interaction.	Interaction unlikely but tramadol can lower seizure threshold.	No apparent clinical effect.	INR is reduced. Dose increase of warfarin often required. Monitor INR in 5–7 days.
	Phenytoin													
	Amiodarone	Potential interaction. Monitor for muscle aches.	Cases of rhabdomyolysis reported. Statin-dose dependent. Monitor for muscle aches, and ALT in 6 weeks.	No reported interactions, but be alert for swollen ankles.	Possible additive effect on myocardial contractility.	No reported interaction, but be alert for swollen ankles.	Possible additive effect on myocardial contractility.	Unlikely interaction.	Unlikely interaction.	Significant increase. Monitor cyclosporin. Be aware of long half-life of amiodarone.	Double digoxin concentration. Monitor digoxin in 2 weeks.		Potential interaction. May prolong sedation. Avoid combination (temazepam likely to be less problematic).	Increase in INR seen in most patients. Monitor INR weekly for 4 weeks (onset seen in ~2 weeks).
	Grapefruit juice	150–250% increase. Avoid combination.	1500% increase. Avoid combination.	Can increase concentrations. Avoid combination.	Can increase concentrations. Avoid combination.	Up to 1200% increase. Avoid combination.	150% increase. Avoid combination.	Unlikely to be important but spotting has been reported.	Unlikely interaction.	Up to 150% increase. Avoid combination.		Unlikely interaction.	150% increase. Avoid combination.	Unlikely interaction.
	Rifampicin		Probable reduction in simvastatin concentration. Monitor lipid profile.	Potential interaction. Monitor blood pressure.	Diltiazem concentrations markedly reduced. Monitor blood pressure and pulse rate.	Limited information, but possible interaction. Monitor blood pressure.	Verapamil concentrations markedly reduced. Monitor blood pressure and pulse rate.	Spotting occurs and 50–70% have menstrual disturbances. Use extra precautions for 4–8 weeks after stopping rifampicin.	Isolated reported of decreased TCA concentrations.	Cyclosporin concentrations likely to be reduced. Monitor cyclosporin.	Serum digoxin concentration can be reduced by 50%. Monitor digoxin concentration in 7–10 days.		Triazolam concentration may be decreased but not temazepam.	INR can be reduced and a dose increase of warfarin required. Monitor INR in 5–7 days.
	St Johns Wort		Probable reduction in concentration – monitor lipid profile.	Potential interaction. Monitor blood pressure.	Potential interaction. Monitor blood pressure.	Potential interaction. Monitor blood pressure.	Potential interaction. Monitor blood pressure.	Interactions reported. Avoid combination.	Serotonin toxicity risk. Avoid combination.	Reduced cyclosporin concentrations. Avoid combination.	Digoxin may be reduced by up to a third. Avoid combination.	Potential risk of serotonin toxicity and increased seizure risk.		Limited cases of reduced INR. Avoid combination.

The coloured text in the table relates to the importance of the interaction:
 RED=Major
 BLUE=Moderate
 GREEN=Minor, if at all
 BLACK=To be aware of

Potential interactions not in the table:

- 'Dangerous Trio' – Diuretics, ACE inhibitor (or Angiotensin II antagonist) plus NSAID (or COX-2 inhibitor). Increased risk of renal failure. **Avoid** or **monitor** renal function in 7–10 days, then in 1 month.
- Warfarin and tramadol. Increased INR is reported. **Avoid** combination. **Monitor** INR in 3–5 days. Regular tramadol is preferable to prn.
- Lithium and ACE inhibitors or diuretics or NSAIDs. Increased lithium concentrations possible. **Monitor** lithium weekly for 2 weeks (NSAID), 6 weeks (ACE Inhibitor), 4 weeks (NSAID).
- Allopurinol and azathioprine. Increased azathioprine concentrations. **Avoid** combination.
- Antibiotics and oral contraceptives. This interaction is very unlikely but due to the consequences using extra precautions is suggested (equates to 7-day rule). Probably more risk with broad spectrum.